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The Cyclization Reaction of Methyl 2-Acyl-4-nitrophenoxyacetates with Potassium Hydroxide

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Methyl 2-acyl-4-nitrophenoxyacetates gave a mixture of the *cis* and *trans* isomers of methyl 3-alkyl-3-hydroxy-5-nitro-2, 3-dihydro-2-benzofurancarboxylates by the reaction with potassium hydroxide in dry dioxane. When the acyl group was acetyl, propionyl, or isobutyryl group, the *cis* isomers (2-methoxycarbonyl group and 3-hydroxyl group are *cis*) were exclusively obtained. On the other hand, a nearly equimolecular amount of the *cis* and *trans* isomers was obtained from the reaction of 2-formyl derivative under the same conditions.

In the Rössing reaction,[1,2] 3-alkyl-3-hydroxy-2, 3-dihydro-2-benzofurancarboxylic acids or their analogues have been considered to be intermediates for the production of benzofurans and 2-benzofurancarboxylic acids.[3-6] However, such intermediates were not isolated at that time because of their high reactivities in acetic anhydride. In this paper, the author reports the synthesis and the stereochemistry of *cis*- and *trans*-2, 3-dihydrobenzofurans obtained by the base-catalyzed intramolecular cyclization of methyl 2-acyl-4-nitrophenoxyacetates (the *cis* isomer is shown by an *cis* relationship between C2 methoxycarbonyl group or carboxyl group and C3 hydroxyl group).

Results and Discussion

The synthesis of methyl esters **1b** and **1d** was carried out according to the reported method.[7] Methyl esters **1a** and **1c** were prepared by esterification of the corresponding carboxylic acids, respectively.

When esters **1a-d** were refluxed with three equivalents of potassium hydroxide in dry dioxane, 2, 3-dihydrobenzofurans (**2a-d** and **3a, b**), ethyl 2-benzofurancarboxylates (**4a-d**), 2-benzofurancarboxylic acids (**5a, b,** and **5d**), and 2, 3-dihydro-2-benzofurancarboxylic acids (**6b-d**) were prepared, respectively. The isolated yield of compounds **2-6** is summarized in Table 1. In the case of ester **1d**, 2, 3-dihydrobenzofuran (**2d**) was obtained in high yield (80%), whereas esters **1a-c** afforded 2, 3-dihydrobenzofurans (**2a-c, 3a,** and **3b**) in poor yields (11-24%), respectively. When esters **1b** and **1c** were refluxed with potassium hydroxide in a 1 : 5 molar ratio, compounds **2b** and **2c** were obtained in high yields (54-56%). The spectral data of **2a-d, 3a,** and **3b** are listed in Table 2.

A mixture of the two isomers **2a** and **3a** (3. 2 : 2 molar ratio) was produced by the treatment of **1a** with base. The structural assignments of the two isomers are as follows. The ^{1}H NMR spectrum of the major component **2a** showed the C2 methine proton signal at δ 5. 29 (d, J=6. 8 Hz) and that of the minor com-

Table 1 The Reaction of Methyl Esters **1a-b** with Potassium Hydroxide in Dry Dioxane

No.	Starting Material 1 (R)	Conditions[a]	Recovery of 1/%	Isolated Yield of Product/%				Total Yield /%
				2 and 3 (2 : 3)	4	5[b]	6[b]	
1	**1a** (H)	A	61	11 (3.2 : 2)	3	2	0	16
2	**1b** (Me)	A	67	24 (18 : 1)	1	1	1	27
3	**1b** (Me)	B	8	54 (14 : 1)	5	—[c]	—[c]	59
4	**1c** (Et)	A	65	20 (1 : 0)	1	0	2	23
5	**1c** (Et)	B	9	56 (1 : 0)	3	—[c]	—[c]	59
6	**1d** (isoPr)	A	8	80 (1 : 0)	2	1	8	91

a) A : 1 : KOH=1 : 3, refluxed for 1 h ; B : 1 : KOH=1 : 5, refluxed for 8 h.
b) Acids **5** and **6** were analyzed as the corresponding methyl esters **4** and **2**, respectively.
c) Compounds **5** and **6** were not analyzed.

Table 2 ^{1}H NMR Spectra and NOE Values (%) of 2, 3-Dihydrobenzofurans (**2** and **3**)

Compound (R)	^{1}H NMR[a,b]		NOE[a,c] (%)
	C2-H	C3-R	[C3-R]C2-H
2a (H)	5.29 (d, $J_{2H,3H}$=6.8 Hz)	5.63 (t)	—
3a (H)	5.20 (d, $J_{2H,3H}$=3.3 Hz)	5.58 (dd)	—
2b (Me)	5.03 (s)	1.88 (s)	33
3b (Me)	5.21 (s)	1.63 (s)	15
2c (Et)	5.09 (s)	0.99 (t), 2.15 (q)	—
2d (isoPr)	5.15 (s)	0.92 (d), 1.08 (d), 2.33 (sept)	—

a) The chemical shifts in ppm down field from internal TMS in $CDCl_3$.
b) Carefully argon degassed solution of **2a, b,** and **3a, b,** were used for the measurement.
c) [C3-R]C2-H denotes obserbation of a NOE of the proton signal on complete saturation of the methyl signal by double irradiation.

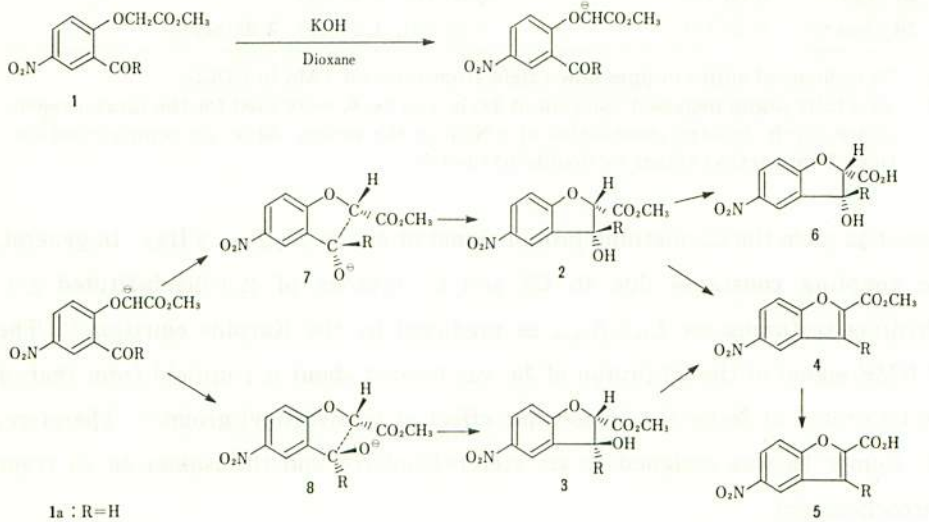
ponent **3a** gave the C2 methine proton signal at δ 5.20 (d, J=3.3 Hz). In general, the coupling constants due to C2 and C3 protons of 2, 3-disubstituted 2, 3-dihydrobenzofurans are $J_{cis}>J_{trans}$ as predicted by the Karplus equation.[8] The ^{1}H NMR signal of the C2 proton of **3a** was located about 0.1 upfield from that of the C2 proton of **2a** by the anisotropic effect of C3 hydroxyl group.[9] Therefore, the isomer **2a** was assigned to *cis* stereochemistry and the isomer **3a** to *trans* stereochemistry.

The methyl ester **1b** afforded a mixture of the two isomers **2b** and **3b** in a 18 : 1 molar ratio. The chemical shift of the C2 methine proton of **3b** is located about δ 0.2 downfield from that of the C2 methine proton of **2a** by the anisotropic effect of C3 methyl group.[10] A large NOE (33%) was observed between C2-H and C3-Me in the product **2b**, whereas a small NOE (15%) was measured in the product **3b**.[11] For these reasons, the major component **2b** was assigned to the *cis* isomer and the minor component **3b** to the *trans* isomer.

Methyl esters **1c** and **1d** gave 2, 3-dihydrobenzofurans **2c** and **2d**, respectively. Only one component of the two isomers was detected with ^{1}H NMR measurement of the products.

The formation of **2a-d** and **3a, b** will be explained in terms of steric effects of R at the cyclization step of **1a-d**, respectively. The reaction of esters **1a-d** with potassium hydroxide is illustrated in Scheme 1. In the case of R=H, an

equimolar amount of **2a** and **3a** was obtained as the steric repulsion between C2 methoxycarbonyl group and C3 hydrogen atom is small. On the other hand, in the case of R=CH_3, the *cis* isomer **2b** was predominantly obtained because the steric repulsion between C2 methoxycarbonyl group and C3 methyl group is large. In the case of R=CH_2CH_3 and $CH(CH_3)_2$, the *cis* isomers **2c** and **2d** must be produced exclusively as the steric repulsion between C2 methoxycarbonyl group and C3 ethyl or isopropyl group in **8c** or **8d** is larger than that in **7c** or **7d**, respectively.



Scheme 1. The cyclization reaction of methyl esters **1a-d** with potassium hydroxide.

Acids **6b-d** were assigned to *cis* stereochemistry by the methylation followed by comparison with authentic samples **2b-d**, respectively.

Experimental

All the melting points are uncorrected. The infrared absorption spectra (IR) were determined on a JASCO IRA-2 spectrometer. The nuclear magnetic resonance spectra (^1H) and nuclear Overhauser effects were determined at 90 MHz on a JEOL JNM-FX 90Q FT NMR spectrometer, using tetramethylsilane as an internal standard. Wakogel C-200 (Wako) was used for column chromatography.

Dry dioxane was prepared by the method of Fieser.[12] Unless otherwise stated, anhydrous sodium sulfate was employed as the drying agent.

A General Procedure for the Reaction of Methyl 2-Acyl-4-nitrophenoxyacetates (**1a-d**) *with Potassium Hydroxide in a* 1 : 3 *Molar Ratio.* A typical procedure is described for the reaction of **1b**. A mixture of **1b** (281 mg, 1.12 mmol), potassium hydroxide powder (181 mg, 3.23 mmol), and dry dioxane (30 ml) was refluxed for 1 h. After cooling, insoluble materials in the reaction mixture were removed by filtration. The residue obtained upon evaporation of the dioxane was dissolved in benzene and insoluble materials were filtered. After evaporation of benzene, the residue (275 mg) was chromatographed on silica gel (30 g). The first fraction eluted with benzene gave 3 mg (1%) of **4b**[7] as crystals. The second fraction eluted with benzen-ether (30 : 1) gave 189 mg (67%) of **1b** as crystals. The third fraction eluted with benzene-ether (20 : 3) gave 68 mg (24%) of a mixture of **2b**[7] and **3b** as crystals. The ratio of **2b** to **3b** (18 : 1) was determined by ^{1}H NMR spectroscopy.

The insoluble materials obtained above were combined and dissolved in water and acidified with 6M hydrochloric acid. The resulting acids were extracted with ether and methylated with diazomethane. The residue (31 mg) obtained upon evaporation of ether was chromatographed on silica gel (15 g). The first fraction eluted with benzen gave the methyl ester of **5b** (2.8 mg, 1%) as colorless crystals, which was identified by comparison with an authentic sample of **4b**. The second fraction eluted with benzene-ether (30 : 1) gave an unidentified compound (12 mg). The third fraction eluted with benzene-ether (20 : 3) gave the methyl ester of **6b** (3 mg, 1%) as crystals, which was identified by comparison with an authentic sample of **2b**.

The results of esters **1a**, **1c**, and **1d** with potassium hydroxide in dry dioxane are listed in Table 1. The reaction of **1b** and **1c** with five equivalents of potassium hydroxide in dry dioxane for 8 h was carried out in a manner similar to that described above and the results are summarized in Table 1. Compounds **2d**, **4a**, **4b**, **4c**, and **4d** were identified by comparison of their IR and ^{1}H NMR spectra with those of authentic samples which were prepared according to the reported procedure.[7]

2c : Colorless short needles from benzene-hexane, mp 115.0-115.5°C. IR(KBr) : ν_{max} 3410 (OH), 1755 and 1744 (CO_2), 1513 and 1338 cm^{-1} (NO_2). ^1H NMR ($CDCl_3$) : δ=0.99 (3H, t, J=7.2 Hz, C3-$CH_2C\underline{H}_3$), 2.15 (2H, q, J=7.2 Hz, C3-$C\underline{H}_2CH_3$), 3.16 (1H, s, OH), 3.82 (3H, s, CO_2CH_3), 5.09 (1H, s, C2-H), 6.99 (1H, dd, J=7.9 and 1.5 Hz, C7-H), 8.18 (1H, dd, J=2.4 and 1.5 Hz, C4-H), and 8.21 (1H, dd, J=7.9 and 2.4 Hz, C6-H). Found : C, 54.14 ; H, 4.95%. Calcd for $C_{12}H_{13}NO_6$: C, 53.93 ; H, 4.90%.

Separation and Identification of cis-*and* trans-2, 3-*Dihydrobenzofurans* (**2a, b** *and* **3a, b**). The *trans* isomer **3a** was obtained by fractional crystallization of the mixture of **2a** and **3a** (3.2 : 2) from ether and then from methanol two times. The *cis* isomer **2a** was obtained by crystallization of the residue obtained by concentration of the ethereal solution from benzene-ether two times.

2a : Pale yellow short needles, mp 146-147°C. IR (KBr) : ν_{max} 3465 (OH), 1724 (CO_2), 1601, 1523 and 1347 (NO_2), 1042, and 824 cm^{-1}. ^1H NMR ($CDCl_3$) : δ= 2.87 (1H, br d, J=6.8 Hz, OH), 3.88 (3H, s, CO_2CH_3), 5.29 (1H, d, J=6.8 Hz, C2-H), 5.63 (1H, br t, J=6.8 Hz, C3-H), 7.05 (1H, d, J=7.0 Hz, C7-H), 8.33 (1H, dd, J=7.0 and 3.0 Hz, C6-H), and 8.37 (1H, d, J=3.0 Hz, C4-H). Found : C, 50.42 ; H, 3.82 ; N, 5.68%. Calcd for $C_{10}H_9NO_6$: C, 50.21 ; H, 3.79 ; N, 5.86%.

3b : Pale yellow short needles from methanol, mp 181-182°C. IR (KBr) : ν_{max} 3440 (OH), 1731 (CO_2), 1602, 1510 and 1345 (NO_2), 1036, 837, 830, and 825 cm^{-1}. ^1H NMR ($CDCl_3$) : δ=2.65 (1H, br d, J=6.8 Hz, OH), 3.84 (3H, s, CO_2CH_3), 5.20 (1H, d, J=3.3 Hz, C2-H), 5.58 (1H, dd, J=6.8 and 3.3 Hz, C3-H), 7.07 (1H, d, J=9.4 Hz, C7-H), 8.28 (1H, dd, J=9.4 and 2.4 Hz, C6-H), and 8.32 (1H, d, J= 2.4 Hz, C4-H). Found : C, 50.49 ; H, 3.81 ; N, 5.72%. Calcd for $C_{10}H_9NO_6$: C, 50.21 ; H, 3.79 ; N, 5.86%.

The *cis* isomer **2b** was obtained by fractional crystallization of the mixture of **2b** and **3b** (18 : 1) from benzene. The *trans* isomer **3b** was obtained by column chromatography of the residue obtained by concentration of mother liquor on silica gel and eluted with benzene-ether (50 : 1).

2b : [7] IR (KBr) : ν_{max} 3415 (OH), 1750 (CO_2), 1599, 1517 and 1336 (NO_2), 1042, 868, 827, and 816 cm^{-1}. ^1H NMR ($CDCl_3$) : δ=1.87 (3H, s, C3-CH_3), 3.08 (1H, s, OH), 3.85 (3H, s, CO_2CH_3), 5.01 (1H, s, C2-H), 7.01 (1H, d, J=9.7 Hz, C7-H),

8.22 (1H, d, J=2.4 Hz, C4-H), and 8.23 (1H, dd, J=9.7 and 2.4 Hz, C6-H).

3b : Crystals, mp 89-90°C. IR (KBr) : ν_{max} 3500 (OH), 1760 and 1750 (CO_2), 1598, 1508, and 1340 (NO_2), 1034, and 837 cm^{-1}. ^1H NMR ($CDCl_3$) : δ=1.63 (3H, s, C3-CH_3), 2.83 (1H, br s, OH), 3.84 (3H, s, CO_2CH_3), 5.21 (1H, s, C2-H), 7.03 (1H, d, J=9.4 Hz, C7-H), 8.19 (1H, d, J=2.5 Hz, C4-H), and 8.22 (1H, dd, J=9.4 and 2.5 Hz, C6-H). Found : C, 52.24 ; H, 4.44 ; N, 5.52%. Calcd for $C_{11}H_{11}NO_6$: C, 52.17 ; H, 4.38 ; N, 5.53%.

Preparation of Methyl 2-Acyl-4-nitrophenoxyacetate (1).

Methyl esters **1b** and **1d** were prepared according to the literature method.[7]

Methyl 2-Formyl-4-nitrophenoxyacetate (**1a**). A mixture of dimethyl acetal of **1a** (5 g) and 50 ml of 5% hydrochloric acid was stirred at room temperature for 4 h. The reaction mixture was extracted with ether. The ethereal solution was washed with cold water and dried. The residue (4 g) obtained upon evaporation of ether was recrystallized from benzene-ether to give 3.3 g (78.6%) of **1a** as colorless short needles, mp 77.0-78.5°C. IR (KBr) : ν_{max} 1754 (CO_2), 1683 (CHO), 1514 and 1350 cm^{-1} (NO_2). ^1H NMR ($CDCl_3$) : δ=3.86 (3H, s, CO_2CH_3), 4.95 (2H, s, OCH_2), 7.04 (1H, d, J=9.0 Hz, C6-H), 8.40 (1H, dd, J=9.0 and 2.9 Hz, C5-H), 8.68 (1H, d, J=2.9 Hz, C3-H), and 10.51 (1H, s, CHO). Found : C, 50.44 ; H, 3.74 ; N, 5.76%. Calcd for $C_{10}H_9NO_6$: C, 50.22 ; H, 3.79 ; N, 5.86%.

Methyl 2-Formyl-4-nitrophenoxyacetate Dimethyl Acetal. A mixture of 2-formyl-4-nitrophenoxyacetic acid[6] (10 g), concd sulfuric acid (5 ml), and methanol (200 ml) was refluxed for 10.5 h. After cooling, the residue obtained upon evaporation of methanol was poured into 200 ml of ice water and extracted with ether (400 ml). The ethereal solution was washed with a 3% potassium carbonate solution and with cold water, and dried. The residue (12 g) obtained upon evaporation of ether was recrystallized three times from methanol to give 5.4 g of the dimethyl acetal as colorless short needles, mp 65.0-67.5°C. IR (KBr) : ν_{max} 1754 (CO_2), 1508 and 1340 (NO_2), and 828 cm^{-1}. ^1H NMR ($CDCl_3$) : δ=3.41 (6H, s, $CH(OC\underline{H}_3)_2$), 3.82 (3H, s, CO_2CH_3), 4.81 (2H, s, OCH_2), 5.72 (1H, s, $C\underline{H}(OCH_3)_2$), 6.84 (1H, d, J=9.0 Hz, C6-H), 8.20 (1H, dd, J=9.0 and 2.8 Hz, C5-H), and 8.47 (1H, d, J=2.8 Hz, C3-H). Found : C, 50.42 ; H, 5.33%. Calcd for $C_{12}H_{15}NO_7$: C, 50.53 ; H, 5.30%.

Methyl 4-Nitro-2-propionylphenoxyacetate (1c).

To an tetrahydrofuran solution of 4-nitro-2-propionylphenoxyacetic acid[6] (4 g), excess diazomethane in ether was added and the solution was allowed to stand at room temperature for 30 min. The residue obtained upon evaporation of ether and tetrahydrofuran was chromatographed on silica gel and eluted with benzene-ether (20 : 1) to give crude 1c. The crude 1c was recrystallized from methanol to give 3.4 g (81%) of 1c as colorless short needles, mp 100.5–101.5°C. IR (KBr) : ν_{max} 1773 (CO_2), 1684 (CO), 1523 and 1352 cm^{-1} (NO_2). ^1H NMR ($CDCl_3$) : δ=1.19 (3H, t, J=7.3 Hz, $COCH_2\underline{CH_3}$), 3.11 (2H, q, J=7.3 Hz, $CO\underline{CH_2}$-CH_3), 3.85 (3H, s, CO_2CH_3), 4.88 (2H, s, OCH_2), 6.95 (1H, d, J=9.2 Hz, C6-H), 8.29 (1H, dd, J=9.2 and 2.9 Hz, C5-H), and 8.56 (1H, d, J=2.9Hz, C3-H). Found : C, 54.21 ; H, 4.80 ; N, 4.99%. Calcd for $C_{12}H_{13}NO_6$: C, 53.93 ; H, 4.90 ; N, 5.24%.

The measurement of NOE was performed as previously described.[7]

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